

Artificial Intelligence in a Mobile Intervention for Depression and Anxiety (AIM)
Short Study Title: IntelliCare Study

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Study Drug/Study Device: IntelliCare (mobile phone based mental health intervention)

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STUDY SUMMARY

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| Full Protocol Title | Artificial Intelligence in a Mobile Intervention for Depression and Anxiety (AIM) |
| Short Title | IntelliCare Study |
| Protocol Number | IRB# STU00074405 |
| Methodology | Phase 1: Intervention development and user testing, Phase II: Field Trial, Phase III: Randomized Controlled Trial. |
| Study Duration | 5 years |
| Study Center(s) | Single-center |
| Objectives | The primary aim of this study is to develop and evaluate the use of state of the art machine learning approaches within a mobile phone intervention application for the treatment of symptoms of depression and anxiety. |
| Number of Subjects | Up to 1,250 participants |
| Diagnosis and Main Inclusion Criteria | Clinically significant symptoms of depression and/or anxiety. |
| Study Product(s), Dose, Route, Regimen | IntelliCare (mobile phone based mental health intervention) |
| Statistical Methodology | The primary outcome will be time to last use of a treatment element (lesson or tool), and will be tested between groups using traditional survival (Kaplan-Meier) methods, where the event of interest is last use from intervention start. |

1 BACKGROUND AND RATIONALE

MDD is common, with 12-month prevalence rates of 6.6-10.3%.(Kessler et al., 2003; Kessler et al., 1994) Depression imposes a very high societal burden in terms of cost, morbidity, suffering, and mortality.(Wells et al., 2002; Whooley & Simon, 2000; Whooley, Stone, & Soghikian, 2000) Psychological treatments are effective in treating depression(Cuijpers, van Straten, Andersson, & van Oppen, 2008), preferred to psychopharmacological treatments by 2/3rds of primary care patients,(Bedi et al., 2000; Churchill et al., 2000; Dwight-Johnson, Sherbourne, Liao, & Wells, 2000; Priest, Vize, Roberts, Roberts, & Tylee, 1996) but inaccessible by 75% of depressed patients.(Mohr et al., 2006; Mohr et al., 2010) Furthermore, 12-month prevalence rates indicate that 21-30 million Americans will require treatment for MDD (and up to 60 million for mental health) each year, needs that we will never be able to meet with standard one-on-one intensive treatments.(Kazdin & Blase, 2011) To meet population needs for mental health treatment, behavioral intervention technologies (BITs), including web-based and mobile interventions, are being integrated into the healthcare systems in Europe(National Institute for Clinical Excellence, 2004; Smit & Riper, 2011) and Australia,(Christensen & Hickie, 2010) as well as care systems in the US including HMOs, employee assistance programs, and the Veterans Administration (VA).(Clarke et al., 2009; Darkins et al., 2008) BITs have been shown to be moderately effective in treating depression, particularly when guided by human coaching via secure in-site email or telephone.(Andersson & Cuijpers, 2009; Ehrenreich, Righter, Rocke, Dixon, & Himelhoch, 2011; Fjeldsoe, Marshall, & Miller, 2009; Heron & Smyth, 2010)

More than 88% of Americans use a mobile phone; 46% use smartphones, a number that is growing rapidly.(Smith, 2012) With their increasing computing power, smartphones are becoming the primary access devices to the Internet,(Smith, 2011) thereby opening the potential for care systems to be continuously connected into the fabric of patients' lives. Mobile interventions for depression have shown promising, albeit generally modest, improvements in many health and mental health problems, including depression.(Agyapong, Ahern, McLoughlin, & Farren, 2012 (in press); Burns et al., 2011; Ehrenreich et al., 2011; Fjeldsoe et al., 2009; Heron & Smyth, 2010) However, mobile- and web-based BITs continue to demonstrate fundamental weaknesses. The lack of personalization, rigid BITs protocols and algorithms, and inability to adapt to patient needs or wants contribute to a perceived lack of relevance, which results in poorer adherence and outcomes.(Strecher, Shiffman, & West, 2006) Tailored interventions produce better outcomes and adherence,(Resnicow et al., 2008) however, to date tailoring has been simplistic and static, focusing on a few patient attributes measured at baseline, with little or no ability to adapt during treatment. Incorporation of machine learning, which can learn from the patient's responses and interactions with the device, can provide an extremely high level of tailoring in patient-specific treatment interventions.

The primary aim of this study is to develop and evaluate the use of state of the art machine learning approaches within a mobile phone intervention application for the treatment of symptoms of depression and anxiety. We will develop an intelligent mobile Behavioral Intervention Technology that utilizes machine learning to tailor treatment content to the patient. Machine learning, a branch of artificial intelligence, focuses on the development of algorithms that automatically improve and evolve based on collected data. Machine learning models can learn to detect complex, latent patterns in data and apply such knowledge to decision making in real time. The intervention, called IntelliCare, is a suite of 14 apps that support skills to improve symptoms of depression and anxiety. These include 13 treatment apps and one "Hub" app that integrates the apps and organizes the user's experience. These apps represent a unique treatment approach. Each app instantiates a single behavioral strategy (e.g. scheduling positive behaviors, thought restructuring, goal setting, etc.), and takes only a few seconds to use. Use of the apps is integrated using a Hub app, that manages notifications and recommendations. In the randomized controlled trial, the IntelliCare machine learning framework will use individual data obtained from app use data (e.g., length of time using a treatment component) and the user's self-reports (e.g., "like" and usefulness ratings of treatment components) to provide a highly tailored intervention that can learn from the patient and adapt intervention and motivational materials to the patient's

preferences and state. Low intensity coaching will serve as a backstop to support adherence.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- 2.1.1 Develop IntelliCare and optimize its functionality through laboratory and field usability testing.
- 2.1.2 Develop the machine learning models and algorithms that will continuously learn from user interactions with IntelliCare to provide intervention recommendations and motivational messaging.
- 2.1.3 Conduct a randomized controlled trial (RCT) comparing 8 weeks of IntelliCare with the machine learning component to 8 weeks of IntelliCare without the machine learning component for the treatment of depression and anxiety. Participants will be evaluated at baseline, week 4, week 8, and at 3- and 6-month post-treatment follow-ups. It is hypothesized that 1) IntelliCare with the recommendations, in contrast to IntelliCare without the recommendations, will produce greater adherence and greater reductions in depressive and anxiety symptoms and 2) IntelliCare with coaching will produce greater adherence and greater reductions in depressive and anxiety symptoms. The primary patient centered outcome will be depression/anxiety severity.

2.2 Secondary Objectives.

- 2.2.1 Exploration of the mediating effects of adherence markers (e.g. time in treatment, app launches, etc.) coaching variables (e.g. message frequency, timing, etc.), and psychological variables (e.g. change in self-report measures) on depression and anxiety outcomes.
- 2.2.2 Exploration of moderating variables on outcomes, such as baseline demographics, baseline characteristics.
- 2.2.3 Explore, optimize, and validate coaching methods.

3 PARTICIPANT ELIGIBILITY

3.1 Inclusion Criteria:

- 3.1.1 Meets criteria for clinically significant symptoms of depression and or anxiety using self-report measures used in screening for depression and anxiety as well as interviewer administered measures.
- 3.1.2 Is familiar with the use of mobile phones
- 3.1.3 Has an Android phone with at least a basic data plan and messaging plan and an operating system sophisticated enough to support the IntelliCare system
- 3.1.4 Is able to speak and read English;
- 3.1.5 Is at least 18 years of age (except in Nebraska where the age of consent is 19).
- 3.1.6 Is a United States Citizen/Resident

3.2 Exclusion Criteria:

- 3.2.1 Has visual, hearing, voice, or motor impairment that would prevent completion of study and treatment

procedures;

- 3.2.2 Is diagnosed with a psychotic disorder, bipolar disorder, dissociative disorder, substance or alcohol dependence, or other diagnosis for which participation in this trial is either inappropriate or dangerous;
- 3.2.3 Is severely suicidal (has ideation, plan, and intent). Although procedures with back-up plans are in place for patients who develop suicidality, the highly experimental nature of this intervention makes enrollment of severely suicidal patients unethical;
- 3.2.4 Participants who have been on an antidepressant or anxiolytic medication with no dose changes for 14 days and do not intend to change the dose will be eligible. Those who have been on the antidepressant for less than 14 days or intend to have their medication optimized will be asked to wait for screening until they meet the 14-day criterion
- 3.2.5 Has used any of the IntelliCare apps more than one time in the last 3 months.

4 STUDY

Procedures/Methods:

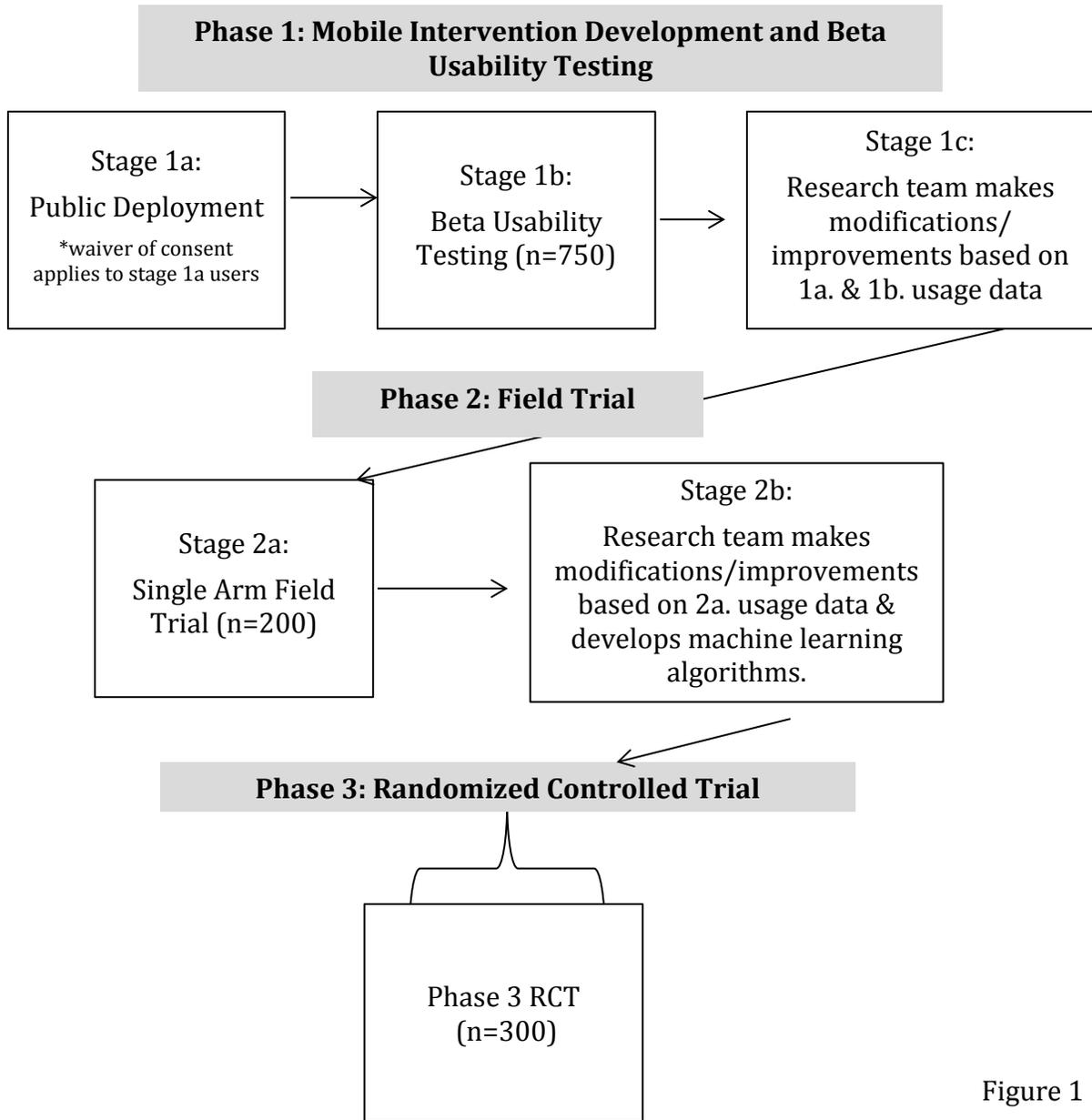


Figure 1

4.1 Recruitment Procedures- All Phases

Participants will be recruited from clinic-based and web-based sites as well as subject recruitment registries and market research companies.

4.1.1.1 Clinic-based recruitment will occur throughout Northwestern Medicine (including but not limited to Cadence Health), The Rehabilitation Institute of Chicago, and the Northwestern REACH program, which is a practice-based research network (PBRN) of primary care clinics in the greater Chicago area. REACH includes two Northwestern primary care clinics and 17 clinical sites including private practices and Federally Qualified Health Centers (FQHCs) with more than 200 member physicians and over 200,000 patients, who are diverse ethnically and economically (see letter of support from REACH director, Dr. Baker). Patients will be recruited via physician referral, fliers in the clinic rooms, and direct recruitment mailings & MyChart messages to patients. Clinic-based recruitment will also be conducted in partnership with Health Partners of Minneapolis, which is a member of the NIMH Mental Health Research Network. Health Partners covers more than 2,000,000 lives. A large percentage of their patients complete the PHQ-9 and GAD-7 on visits to their primary care clinics, allowing for targeted recruitment strategies. HealthPartners patients with elevated symptoms of depression and anxiety will be recruited with email invitations sent via MyChart.

4.1.1.2 Internet-based advertising will ensure that recruitment reflects the growing numbers of people who seek help through the Internet, thereby enhancing external validity. Eligible participants will be recruited using a mass-scale, ongoing recruitment campaign across mainstream Web-based social media sites. A standalone recruitment site will be promoted using graphically designed advertisements on Facebook, Google Adwords advertisements, Reddit and Twitter posts and other social media sites. Further, we have found many health advocacy and support organizations are eager to improve access to services for members and are therefore willing to highlight research studies on their websites and in newsletters. This type of online outreach has been useful in recruiting in previous studies.

4.1.1.3 Participants may be recruited through one of the following **research registries**:

4.1.1.3.1 Research Match: Research Match, a site designed to bring research volunteers and researchers with active research projects, will also be used to recruit participants, along with, mental health advocacy and support organizations such as the Depression and Bipolar Support Alliance. Research Match is a service utilized by 80,000+ volunteers and 3,000+ researchers from 110 institutions.

4.1.1.3.2 Northwestern University NUCATS Registry: The NUCATS General Research Registry will be used as a recruitment method. The NUCATS General Research Registry consists of individuals who have indicated that they are interested in being contacted to participate in research studies occurring at Northwestern University. People can join the NUCATS Registry in one of three ways.

- 1) If the person is a patient at Northwestern Memorial Hospital or an NU affiliate, they can opt-in by logging into MyChart and signing up for MyResearch.
- 2) The person can call the NU Study telephone line and be added to the registry.
- 3) The person can be added to the registry when they screen fail for a study but want to be contacted for future studies.

Individuals in the registry are contacted once a year to update their information. Individuals that indicate that they are no longer interested in being in the registry are removed and are no longer contacted.

- 4.1.1.3.3** CBITs Research Subject Recruitment Registry: CBITs also has an IRB approved registry (STU # STU00076804) through which participants may be contacted
- 4.1.1.4** Market Research Companies: We intend to contract with market research firm, Focus Point Global, to recruit panelists in their database to participate in the Phase 3 RCT.

PHASE 1: MOBILE INTERVENTION DEVELOPMENT AND BETA USABILITY TESTING

- 4.1.2** Phase I – Mobile Intervention Development & Beta Usability Testing (approximately N=750). The overarching goal of this phase is to develop a prototype of the IntelliCare intervention and conduct beta usability testing. Beta usability testing will ensure that the intervention is functional, intuitive and easy to use.

Phase 1 is iterative and includes two stages: (1a) Public deployment, and (1b) Beta Usability Testing. Both stages are designed to elicit information regarding the functionality and usability of the mobile application prior to deployment of any versions of IntelliCare in the Phase 2 Field Trial.

The goal of stage 1a is to collect data from diverse users that will (1) confirm that the mobile apps are functioning (not crashing) across a wide range of android devices and operating systems, (2) provide basic information about app usage and user satisfaction (3) inform the development of reinforcement learning models and (4) collect quality assurance data that will allow the research team to refine the applications. The research team stopped consenting public deployment users when the Northwestern Biomedical IRB approved a waiver of the consent process in February 2015. The goal of stage 1b is to collect feedback from users with symptoms of depression about perceived usefulness and user satisfaction. Data collected during stages 1a and 1b will ultimately will lead to improvements in the design of the IntelliCare system. Beta testers may or may not need to meet inclusion criteria dependent on the stage of the beta testing process.

Usability testing is an iterative process in which groups of participants evaluate application features, problems are identified, fixes are made, and a new round of participants are brought in to evaluate the application. The IntelliCare intervention will be made up of approximately 15 mini applications. As each application is developed, we will make an early prototype available to the general public via the Google play store and consent approximately 200 individuals to participate in stage 1a. usability testing (procedures described in section 6.1.2.2 below). Data collected from stage 1a users will lead to functional improvements. Next, modifications made as a result of 1a usability testing will be evaluated with 50 individuals with at least mild symptoms of depression during stage 1b. Feedback from stage 1b testers will be used to optimize IntelliCare for individuals experiencing symptoms of depression. We will repeat stage 1a (n=200) and stage 1b (n=50) beta testing procedures as each IntelliCare mini app is developed over the course of 12 months.

- 4.1.2.1** Stage 1a: Public Deployment

Stage 1a. During stage 1a individuals in the general public may download IntelliCare apps from the Google play store onto their own Android mobile devices. Stage 1a. users do not need to meet inclusion criteria to use the apps and contribute data for quality assurance/quality improvement purposes. Users will be presented with a user acknowledgement form describing data that may be

collected by the the mobile app. Users must read the acknowledgment before they can proceed to app installation. Users who do not wish to contribute their use data may uninstall the application.

4.1.2.2 Stage 1a users may be offered the opportunity to participate in later phases of the IntelliCare study. As such, after the user acknowledgment is displayed, users will encounter a screen where they will have the option to provide their email address and telephone number to receive information regarding additional research opportunities. Public deployment users will be asked to complete a series of short questionnaires assessing demographics, motivating for downloading the application and mood. The assessments are brief (less than 5 mins). Stage 1a users will not be compensated for using the application(s). All questionnaires will be administered through the mobile application. We will collect basic *demographic information* and ask about the users motivation for downloading the app at baseline. *Self-Reported Depression and Anxiety* will be measured using the 4 item PHQ4. *Application Usage* will be assessed through data collected by the phone, including phone and application usage patterns. This may include information regarding participant use of IntelliCare applications and use of other applications installed on the phone. Only data related to how and when apps are used will be collected and the format in which it is stored will contain no identifying information about users. Information collected from the applications on the mobile phones will be transmitted to a secure server via encrypted, password-protected tunnels to protect users' privacy. Furthermore, the information saved on the server will only be accessible to people provided with the proper credentials (members of the research team, research collaborators, and the users themselves).

4.1.2.3 Stage 1b. Beta Usability Testing (Approximately N=750)

4.1.2.3.1 Stage 1b Enrollment. Approximately 750 adults (50 for each of the 15 IntelliCare mini applications) will be recruited to participate in stage 1b testing. Testers may or may not need to be depressed as per inclusion criteria 3.1.1. Individuals meeting criteria for at least mild symptoms of depression (as determined by PHQ8 score greater than or equal to 10, -OR- GAD7 greater than or equal to 8) will be enrolled. Participants in stage 1b will be enrolled remotely to avoid excluding participants with access barriers who are among those who would be likely end users. Participants will be sent a link to an online consent form. Once consent is signed, eligibility questionnaires will be administered to participants via a secure web based assessment portal, so that other inclusion and exclusion criteria can be determined. If eligible, a participant will be provided a link from which they can download IntelliCare apps onto their own compatible device. This will allow the study to collect data on how patients use the phone application in their daily life, and on their own phone.

4.1.2.3.2 *Stage 1b Assessment:* Participants in stage 1b may participate in telephone or web chat interview evaluations and complete online self-report questionnaires at baseline and when they've completed using each mini app. Those who complete the brief interview and online questionnaire will be compensated \$10 for application they review. Participants can earn between \$10-\$150 (\$10 for each of 15 app reviews) for their involvement in this phase of the study. Participants in the Chicagoland area may also be invited to participate in an in-person usability session lasting up to 90 minutes which involves performing a series of tasks involved in the operation of the application in the presence of research staff. All sessions are videotaped for subsequent team review, as necessary. Participants will be asked to 'think aloud' or provide a running commentary while operating the phone and application, which is a common approach to usability testing that permits investigators to evaluate the ease with which the system is learned and provides first-hand information about design problems. User phone usage will be directly captured on the phone and will be recorded using a video camera. Study staff may contact these participants by phone or email as they use the phone application, to ensure it is easy to use and working properly. Those who are invited to participate in an in-person usability session will be compensated \$40 per usability session completed. Since it may be possible for participants to evaluate the mini apps in as many as 3 distinct usability sessions,

compensation will range from \$40-\$120. In the event a participant is invited to complete all three in-lab usability sessions, as well as view all 15 applications in the field, the participant could then potentially be compensated up to \$270 for his/her feedback. Payments may be made in either Amazon credits or by check depending on participant preference, NU payment policies, and payment availability at the time of study participation.

4.1.2.3.3 *Stage 1b Measures:* Stage 1b usability testers will complete all measures outlined in stage 1a. In addition, stage 1b will include measures of *Affect* measured by the PHQ-8 & GAD-7, *Motivation* measured by the Treatment Self-regulation Questionnaire (TSRQ), and (3) *Stress Management Style* measured by the Measure of Current Status (MOCS) and the Tactics for Coping with Stress Inventory (TCSI). We will also collect data about current and past treatment for depression and mobile phone preferences and usage. We will use standard validated measures to assess user satisfaction measured by the USE survey. Additional information will be collected through a qualitative usability interview designed to elicit feedback about technical problems, ease of use, satisfaction & overall usefulness for various components of the intervention.

PHASE 2: FIELD TRIAL

4.1.3 Phase II – Field Trial. The purpose of the field trial will be twofold. The field trial will extend usability testing over time and under real life conditions. In addition, the field trial will be used to collect data to develop and evaluate machine learning methods. IntelliCare will be evaluated in up to 200 individuals meeting inclusion criteria in a 8-week, single arm field trial.

4.1.3.1 *Phase II Enrollment.* Participants in the field-trial will be enrolled remotely to avoid excluding participants with access barriers who are among those who would be likely end users. Interested parties will complete a brief telephone or web screen to determine whether there is any reasonable expectation that they might be eligible (data from the brief screen will be included in the study dataset). If they are clearly not eligible they will be informed of this and thanked. If they are eligible they will initiate the consent process. Following the initial pre-consent screening phone call but prior to the eligibility interview, the participant will be emailed a link to the detailed digital version of the consent form. Subjects agree to participate by checking a yes box and typing in their name. They are instructed to print out the consent form for their records. After the study consent form is signed online, detailed information regarding the consent will be reviewed with the participant and witnessing of the consent form will take place at this time by study staff. A date and time for the screening assessment will then be scheduled. An RA will then conduct an eligibility interview with the participant over the phone, where the MINI, HAM-A, and QIDs are administered. Questionnaires will be administered to patients via a secure web based assessment portal, so that the other inclusion and exclusion criteria can be determined. Patients will be paid \$20 for completing the eligibility interview. Payments may be made in either Amazon credits or by check depending on participant preference, NU payment policies, and payment availability at the time of study participation.

If eligible, a research study assistant will work with participants to download the IntelliCare system from the Google Play store. Eligible participants will include those who already own an Android smartphone with an operating system sophisticated enough to support the IntelliCare system (version 4.2.2 or higher).

4.1.3.2 *Phase II Treatment* Participants will receive the IntelliCare intervention, which consists of access to apps that address specific treatment goals, and may include didactic content as well as interventional components (e.g. activity scheduling/monitoring, thought records, etc.) that support behavior change. App use is supported by BA level coach (supervised by a licensed psychologist), for 8 weeks. All patients will receive access to this low intensity coaching, which may be delivered via phone call and secure messaging focused on adherence to IntelliCare. At the end of the 8 week trial, participants will be informed that they may continue using the IntelliCare system on their phones but will no longer

have access to their coach. For any participants who do continue their use after the study period has ended, the IntelliCare system will continue to collect phone and app data as before.

- 4.1.3.3** *Phase II Assessment, Measures & Compensation.* Participants in the field trial will receive telephone-based interview evaluations and complete online self-report questionnaires at baseline, week 4 and week 8. All assessments and evaluations will be conducted by an RA who is blind to the treatment (i.e. coaches will not perform assessments on patients they coach). *Depression* will be measured at baseline by telephone interview using the QIDS-C for severity of symptoms and the MINI MDE module for diagnosis. Self-reported depression will be measured at baseline, wk4 & wk8 using the PHQ-9 administered online. *Anxiety* will be measured by telephone interview using the HAM-A for severity of symptoms at baseline. Self-reported anxiety will be measured using the GAD-7 administered online at baseline wk4, and wk8. *Adherence* will be assessed through use data from phone or other platforms (e.g. computer), including number of times the program was accessed, number of times each lesson, tool, and feedback element was accessed and percentage of messages viewed. The first 20 participants will also be engaged in extended usability testing, and will speak with a research assistant weekly, who will inquire into usability problems. We will compensate \$70 to each of the 200 field trial participants for taking part in their follow up assessments (Week 4 and Week 8). Participation in the trial may include the use of texting, and as such, study staff will reimburse participants who do not already have an unlimited monthly texting plan for their upgrade to such. Reimbursement of up to \$30 per month enrolled in the trial (up to two months) is possible. We will not be compensating participants who already subscribe to unlimited texting in their monthly plans. This decision was made in attempt to make the intervention more generalizable, so as not to over-incentivize certain users by compensating them for matters already routine to them. Payments may be made in either Amazon credits or by check depending on participant preference, NU payment policies, and payment availability at the time of study participation.
- 4.1.3.4** *Phase II Data Collection.* Once downloaded, IntelliCare applications will begin collecting data from participants based on their phone and application usage patterns. This may include information regarding participant use of IntelliCare applications, use of other applications installed on the phone, and information about how participants use their phone (e.g., calls, text messages, and internet browsing activities). Only data related to how and when phones and apps are used will be collected and the format in which it is stored will contain no identifying information about participants. Information collected from the sensors and applications on the mobile phones will be transmitted to a secure server via encrypted, password-protected tunnels to protect participants' privacy. Furthermore, the information saved on the server will only be accessible to people provided with the proper credentials (members of the research team and the users themselves).
- 4.1.3.5** *Phase II Study Retention.* Communication from the research study may occur across a participant's involvement in the trial to increase participant retention. Such contact would be limited (e.g. sending

greeting cards via mail or email (thank you, birthday, etc.) or sending small tokens of appreciation (keychains, pens, stress balls).

PHASE 3 RANDOMIZED CONTROLLED TRIAL

- 4.1.4** Phase III – Randomized Controlled Trial. For the RCT, 300 participants meeting entry criteria will be enrolled over 13 months (approximately 23 per month). Participants will be randomized using a factorial design with the following factors:
- 4.1.4.1** Factor 1. Hub App with intelligent recommender system/Hub app without intelligent recommender system: This factor is consistent with Objective 2.1.3 on pg. 4
- 4.1.4.2** *Factor 2. Coaching/No Coaching:* This factor would allow us to examine and control for the effect of coaching.
- 4.1.5** *Phase III Enrollment.* Participants in the RCT will be enrolled remotely to avoid excluding individuals with access barriers who are among those who would be likely end users. Screening will be conducted in 3 stages.
- 4.1.5.1** Screening Stage 1 (pre-consent): Interested parties will complete a brief web screen to determine whether there is any reasonable expectation that they might be eligible (data from the brief screen will be included in the study dataset). If they are clearly not eligible they will be informed of this and thanked. If they appear to be eligible a research assistant will follow-up by phone to clarify responses from the web screen and ask additional phone screening questions. If the participant passes the stage 1 phone screen s/he will be invited to initiate the online consent process and proceed to screening stage 2 described below.
- 4.1.5.2** Online Consent/Screening Stage 2: The participant will be emailed a link to the detailed digital version of the consent form which will be deployed through REDcap or another secure online survey system. Subjects will read through the consent form, answer a series of questions to assess comprehension, and agree to participate by checking a box, typing in their name, and signing electronically. After the online consent form is submitted, participants will continue on to complete a set of baseline questionnaires which will further assess study eligibility. Once the questionnaires are submitted, study staff will review the participant’s digital file to (1) ensure that the consent form was signed and the comprehension questions were answered correctly and (2) make an eligibility determination based on the questionnaire responses. If a participant answers any of the consent comprehension questions incorrectly, a research assistant will follow up to review that section of the consent form and explain the correct answer. Participants may contact study staff at any time for a copy of the consent form for their records. All participants who complete screening stage 2 will be notified regarding eligibility by phone or email. Ineligible participants will be thanked, sent a resource guide and compensated \$10 for completing the online questionnaire. Individuals who are deemed eligible based on responses to the stage 2 screening questions will proceed to screening stage 3 described below.
- 4.1.5.3** Screening Stage 3: Individuals will be contacted to schedule a date and time for the baseline interview. An RA will then conduct the baseline interview with the participant over the phone, where the MINI interview will be administered. All participants who complete the MINI interview will be compensated \$10 for completing the stage 2 screening questionnaires and an additional \$30 for completing the MINI interview. Payments may be made in either Amazon credits, by check or through Paypal depending on referral source, participant preference, NU payment policies, and payment availability at the time of study participation). Participants who are deemed ineligible after the MINI

interview, will be thanked, sent a resource guide and compensated. If eligible following the MINI interview, participants will be randomized and enrolled in the study.

4.1.5.4 Study Enrollment: A research study assistant will work with participants to download the IntelliCare apps from the Google Play store, and if assigned to work with a coach, schedule the coach orientation call.

4.1.6 *Phase III Treatment Plan.* The IntelliCare intervention will be comprised of a combination of 3 components: (1) IntelliCare Treatment Apps, (2) IntelliCare Hub App, (3) and Coaching. A brief description of each component appears below.

1. IntelliCare Treatment apps: There are 13 IntelliCare treatment apps. Each app instantiates a single behavioral strategy (e.g. scheduling positive behaviors, thought restructuring, goal setting, etc.), and takes only a few seconds to use. The apps address specific treatment goals, and may include didactic content as well as interactional components (e.g. activity scheduling/monitoring, thought records, etc.) that support behavior change. All participants will download the apps onto their own phones and use them daily during the 8 week intervention period.
2. IntelliCare Hub app: The “Hub” app integrates the treatment apps and organizes the user’s experience. We will be testing two different versions of the hub app; one with an intelligent recommender system (version A) and one without (version B). The recommender system in version A will use machine learning, which can learn from a patient’s interactions with the intervention, to deliver and adapt treatment to the needs and preferences of the participant.
3. Coaching: BA level coaches (supervised by a licensed psychologist), may support participants throughout the 8 week intervention period. We have developed a low-intensity coaching model that relies primarily on brief text messaging to promote engagement, along with one engagement orientation call at the beginning of treatment, and the option of a second call if needed.

While **all** participants will have access to the treatment apps during the 8-week intervention period, the version of the Hub app and the inclusion of coaching will vary for each participant according to random assignment to one of 4 groups:

Group 1 (n=75): Hub App Version A + Treatment Apps + Coaching

Group 2 (n=75): Hub App Version A + Treatment Apps + Independent Use (no coaching)

Group 3 (n=75): Hub App Version B + Treatment Apps + Coaching

Group 4 (n=75): Hub App Version B + Treatment Apps + Independent Use (no coaching)

At the end of the 8 week intervention, all participants will be informed that they may continue using the IntelliCare system on their phones but participants in groups 1 and 3 will no longer have access to their coach. For any participants who do continue app use after the study period has ended, the IntelliCare system will continue to collect app data as before.

4.1.6.1 *Phase III Assessment, measures and compensation.* RCT participants will receive trial assessments at baseline, week 4, and week 8 (post-treatment). Post-treatment follow-up evaluations will occur at 3 and 6 months to evaluate maintenance of gains. Assessments will consist of telephone based interviews and online self-report questionnaires. All assessments and evaluations will be conducted by an RA (i.e. coaches will not perform assessments on patients they coach). *Depression* will be measured at baseline by telephone interview using the MINI MDE module. Self-reported depression will be measured at baseline, wk4, wk8, 3 months post-treatment and 6 months post-treatment using the PHQ-9 administered online. Self-reported anxiety will be measured using the GAD-7 administered online at

baseline wk4, wk8, 3 months post-treatment and 6 months post-treatment. *Adherence* will be assessed through app use data from phone, including number of times the apps were accessed, number of times each app feature was accessed and percentage of messages viewed. Participants will be paid up to \$40 for the screening/baseline assessments, \$30 for the week 4 and 8 assessments, and \$30 for the 3 and 6 month assessments (total= up to \$160). Participants will not be compensated for using the apps or communicating with the study coach. Payments may be made in either Amazon credits or by check depending on participant preference, NU payment policies, and payment availability at the time of study participation. Individuals recruited through Focus Pointe Global will be paid through PayPal by Focus Pointe Global.

4.1.7 *Phase II Study Retention.* Communication from the research study may occur across a participant's involvement in the trial to increase participant retention. Such contact could include sending greeting cards via mail or email (thank you, birthday, etc.) or sending small tokens of appreciation (keychains, pens, stress balls).

4.2 Confidentiality of Records- all phases

Study data will be kept in a locked, password protected databases stored on secure servers maintained by Northwestern University FSM IT. Participants' direct personal identifiers will not be released without prior consent except as specifically required by law. Efforts will be made to limit the use and disclosure of research study data to people who have a need to review this information. Study data may be shared for research purposes with collaborators outside of the research team at Northwestern University. Collaborators may include researchers at other institutions such as universities, foundations, research groups within companies, and/or government agencies for the purposes of improving the science by aggregating datasets across projects or accessing specialized expertise such as machine learning and data mining. A data use agreement will be established before study data is released to a researcher or organization that is not part of the study team. The data use agreement will specify what data will be transferred to another organization or research (see list of Data below). Some journals now require that data used in publications must be provided to the journal and may be made public. In those instances, we will provide a de-identified dataset to the journal. Study consent forms will explain the range of information that may be shared with collaborators.

4.3 Data

4.3.1.1.1 *Adherence:* The primary adherence outcome will be length of time from initiating treatment to last use of treatment elements. We will also explore the motivational system by examining the number of motivational messages delivered, number viewed and the ratio of viewed/delivered by treatment arm. More specifically:

4.3.1.1.1.1 Messages include text and email messages between participants and study staff for the purposes of coaching and participant management.

4.3.1.1.1.2 App use includes the number, timing, and duration, application launches and launches of specific pages within the app.

4.3.1.1.2 *Depression:* Primary patient centered outcomes will use continuous measures of depression and anxiety.

4.3.1.1.2.1 *PHQ-9* will be used to evaluate self-reported depression. *GAD-7* will be used to evaluate self-reported anxiety.

4.3.1.1.3 *Secondary Outcome Measures* will include the following (for a full list of self-report measures see Measures Appendix):

4.3.1.1.3.1 *Satisfaction*, measured using the USE questionnaire, which was designed to measure satisfaction, usefulness, ease of use, and ease of learning.

Moderators and mediators will include the measures provided prior to initiating treatment the Mini International Neuropsychiatric Interview, the SCT Motivation assessment, Behavioral Activation, well-being and quality of life, Coping, and

4.3.1.1.3.2 Audiofiles include audio recordings of coaching and assessments. Audio files may be transcribed by one or more of the following NU transcription vendors:

GMR Transcription <https://www.gmrtranscription.com/>

Wordsworth <https://wordsworthcoop.com>

Files may be shared via secure access to FSM servers or through vendors' proprietary web-based applications for secure file management.

4.3.1.1.4 Coach generated notes on participant encounters.

4.4 Removal of Subjects from Study

Patients can be taken off the study treatment and/or study at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation will be documented and may include:

4.4.1 Patient voluntarily withdraws from treatment (follow-up permitted);

4.4.2 Patient withdraws consent (termination of treatment and follow-up);

4.4.3 Patient is unable to comply with protocol requirements; (termination of treatment and follow-up);

4.4.4 Patient demonstrates disease progression (termination of treatment and follow-up unless continued treatment with study intervention is deemed appropriate at the discretion of the investigator);

4.4.5 *Identification of Suicidality.* Suicidality will be monitored at all possible points of contact. It will be monitored by RAs at each assessment point (Field Trial: Baseline, Week 6, and Week 12. RCT: Baseline, Week 6, Week 12, Month 3, Month 6), using the QIDS-C and MINI module(s). Report of an elevated level of suicidal ideation (MINI Suicidality module score of 8 or greater or QIDS question 12 response of 12 score of 2 or greater at baseline; Positive response for MINI MDE section question A3.g or QIDS question 12 score of 2 or greater during later time points) will trigger administration of the CBITS Suicidality Protocol by the RA. Following a structured assessment of suicidal ideation by an RA, the information will be provided to a clinical monitor (Ph.D. level psychologist) who will review the information and take appropriate action (see below). One Ph.D. psychologist will be designated as

clinical monitor at all times. . Suicidality will also be monitored in online self-report assessments. A score of 2 or greater on the PHQ-9 item 9 branches to the BDI-I item 9, which assesses for severity of suicidal ideation. Scores of 2 or greater on the BDI-I item 9 will trigger automatic and immediate notification to the RA who will attempt to contact the participant by phone, complete the CBITS Suicidality Protocol with direction and supervision by the Ph.D level clinical monitor as needed. Additionally, Coaches will be trained to identify potential suicidality in the coaching engagement telephone call or secure email communications, which will similarly result in administration of the CBITS Suicidality Protocol.. Information about suicidality will be discussed with the clinical monitor.

- 4.4.6** *Ensuring patient safety.* Once the monitor (or any study clinician, who will serve as the monitor) is notified of potential suicidality, the monitor will take all actions necessary to ensure patient safety. This includes: evaluation of all necessary data including study records, calling the patient for further evaluation, recommending hospitalization, calling emergency services in the participant’s jurisdiction to perform a “health and safety” check, or any other actions deemed necessary to ensure the safety of the patient. The monitoring clinician also has the option of recommending that the patient be discontinued from the study and referred for more appropriate care. Because RAs are usually the main point of contact for patients, they will be given thorough training in the assessment of suicidality. While the clinical monitors will be responsible for the management of suicidal patients, it is possible that an emergent situation will arise that requires immediate attention. RAs (assessors and coaches) will be trained in the use of the CBITS Suicidality Protocol. This document includes a well-validated measure for assessing suicidal risk (Columbia Suicide Severity Rating Scale) and structured follow-up steps based on the participants’ reported score. RA’s will also standardly collect information regarding participants’ current location when contacting the participant by phone in the case there is a need to contact emergency services. The PI will also be notified of all cases of suspected suicidality, will consult with the clinical monitor, and will be continuously updated. Any psychiatric problem rising to the level of an adverse event will be reported to the IRB and to the DSMB chair.
- 4.4.7** *Patient Deterioration.* Clinical deterioration as evidenced by an increase in the severity of depressive or psychiatric symptoms is the other potential risk. If the RA believes that a participant has deteriorated substantially either by showing a worsening in the presenting psychiatric symptoms or by the development of new psychiatric or treatment related symptoms, the clinical monitor will immediately be informed. The clinical monitor will evaluate the participant, notify the PI and DSMB, and make any necessary referrals for the care of the participant. If the PI, in consultation with the DSMB, determines it is in the participant’s best interest to cease participation in the study, the patient will be terminated from the study, and referrals and assistance will be given in obtaining appropriate treatment. Reports will be filed with all necessary governing bodies, including the Northwestern University IRB and the DSMB.
- 4.4.8** Treating physician judges continuation on the study would not be in the patient’s best interest;
- 4.4.9** Lost to follow-up. If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered “lost to follow-up.” All attempts to contact the subject during the two years must be documented and approved by the Data Monitoring Committee.

5 Adverse Event Monitoring

- 5.1.1** Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of Subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal

monitoring of patient safety and care.

- 5.1.2 All patients experiencing an adverse event, regardless of its relationship to study drug/device, will be monitored until:
 - 5.1.2.1 the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
 - 5.1.2.2 any abnormal assessment ratings/observations have returned to baseline;
 - 5.1.2.3 there is a satisfactory explanation other than the study intervention for the changes observed; or
 - 5.1.2.4 death.

5.2 Definitions

- 5.2.1 Definition of Adverse Event. An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory

finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

5.2.2 Severity of Adverse Events. The severity of an AE is graded as follows:

5.2.2.1 Mild (grade 1): the event causes discomfort without disruption of normal daily activities.

5.2.2.2 Moderate (grade 2): the event causes discomfort that affects normal daily activities.

5.2.2.3 Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.

5.2.2.4 Life-threatening (grade 4): the patient was at risk of death at the time of the event.

5.2.2.5 Fatal (grade 5): the event caused death.

5.2.3 Serious Adverse Events. A “serious” adverse event is defined in regulatory terminology as any untoward medical occurrence that:

5.2.3.1 Results in death. If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

5.2.3.2 Is life-threatening. (the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).

5.2.3.3 Requires in-patient hospitalization or prolongation of existing hospitalization for ≥ 24 hours.

5.2.3.4 Results in persistent or significant disability or incapacity.

5.2.3.5 Is a congenital anomaly/birth defect

5.2.3.6 Is an important medical event

5.2.3.7 Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of “Serious Adverse Event“. For example: allergic bronchospasm requiring intensive treatment in an emergency room or at

home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

5.3 Steps to Determine If an Adverse Event Requires Expedited Reporting

5.3.1 Step 1: Identify the type of adverse event

5.3.2 Step 2: Grade the adverse event

5.3.3 Step 3: Determine whether the adverse event is related to the protocol therapy

5.3.3.1 Attribution categories are as follows:

5.3.3.1.1 Definite – The AE *is clearly related* to the study treatment.

5.3.3.1.2 Probable – The AE *is likely related* to the study treatment.

5.3.3.1.3 Possible – The AE *may be related* to the study treatment.

5.3.3.1.4 Unrelated – The AE *is clearly NOT related* to the study treatment.

5.3.3.1.5 Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

5.3.4 Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:

5.3.4.1 the current known adverse events listed in the Agent Information Section of this protocol;

5.3.4.2 the drug package insert;

5.3.4.3 the current Investigator's Brochure

5.4 Reporting Requirements for Adverse Events

5.4.1 Expedited Reporting. The Principal Investigator must be notified within 24 hours of learning of any serious adverse events, regardless of attribution, occurring during the study or within 30 days of the last administration of the study drug.

5.4.2 Routine Reporting. All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

6 STATISTICAL CONSIDERATIONS

6.1 Public Deployment

6.2 Adherence Outcomes:

6.3 The primary outcome of Phase 1a will be rate of usage of each Intellicare application. This will be

examined by calculating standard descriptive statistics for the number of downloads and launches of each application. Secondary analyses of the primary outcome will include comparisons of co-usage of Intellicare application pairs, which we will test using Pearson correlations.

6.4 Field Trial

6.5 Power/sample size:

6.5.1 We estimate that we will have a 20% dropout, which will give us 80% power to detect effect sizes of 0.30. Power calculations were performed using Pass 2008.(Hintze, 2008)

6.6 Adherence Outcomes:

6.6.1 The primary outcome will be time to last use of a treatment element (lesson or tool), and will be tested between groups using traditional survival (Kaplan-Meier) methods, where the event of interest is last use from intervention start. Secondary analyses of the primary outcome would include Cox regression models that would adjust for potential effect modifiers or moderators such as gender, race, and age.

6.7 Patient Centered Outcomes:

6.7.1 Although power was presented for independent t-tests, primary analyses for patient centered outcomes (PHQ-9 and GAD-7) will utilize dependent t-tests

6.8 Mediation Analyses:

6.8.1 Mediators, such as app usage, will be examined in mediation models as time-varying covariates. We used the framework of Muller and colleagues(Muller, Judd, & Yzerbyt, 2005) to identify those variables, which mediate the effects of treatment on depression and anxiety. Only if the 4 criteria specified by Muller are satisfied (treatment effect for depression, treatment effect for the mediator, effect of mediator on depression, and reduction of treatment effect when mediator is included), will we calculate the effect of mediation using MacKinnon and colleagues' product of coefficients method.(MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) Bias-corrected 95% confidence intervals for the mediated effect will be calculated using bootstrapping.(Shrout & Bolger, 2002)

6.8.2 Development of the recommendation engine algorithms will use machine learning and Bayesian statistical methods that will continuously learn from user interactions with IntelliCare to provide intervention recommendations.

6.9 Randomized Control Trial

6.9.1 Power/sample size:

6.9.2 Preliminary data indicates that approximately 50% of patients stop participating in BITs (which we define here as “drop out”) by week 7 (see Sec. D.1.1). A sample size of 135/arm (total sample of 270) will provide 80% power to detect a difference in median drop out time from 7 to 10 weeks. We estimate from existing data (Sec D.1.1) that a 3 week increase would result in an 11% improvement in depression severity (ES=0.30). Additionally, this sample provides 80% power to detect an increase in continued participation from 50% to 61.6% at week 7. Both analyses are based on a log-rank test at a type 1 error rate of 5%, with accrual of 54 weeks and 12 weeks of intervention. Power for continuous patient

centered outcomes were based on independent t-tests, and would have 80% power to detect effect sizes of 0.34. Power calculations were performed using Pass 2008.(Hintze, 2008)

6.10 Adherence Outcomes:

6.10.1 The primary outcome will be time to last use of a treatment element (lesson or tool), and will be tested between groups using traditional survival (Kaplan-Meier) methods, where the event of interest is last use from intervention start. Secondary analyses of the primary outcome would include Cox regression models that would adjust for potential effect modifiers or moderators such as gender, race, and age.

6.11 Patient Centered Outcomes:

6.11.1 Although power was presented for independent t-tests, primary analyses for patient centered outcomes (QIDS-C, MDD, and PHQ-9) will utilize generalized linear mixed (GLM) models (with link functions depending on the distribution of the outcome), that can examine patterns over the course of treatment and follow-up, and can account for missing data.(Gibbons et al., 1993)

6.12 Secondary Mediation Analyses:

6.12.1 Mediators will be entered into our models as time-varying covariates. We used the framework of Muller and colleagues(Muller, Judd, & Yzerbyt, 2005) to identify those variables, which mediate the effects of treatment on depression. Only if the 4 criteria specified by Muller are satisfied (treatment effect for depression, treatment effect for the mediator, effect of mediator on depression, and reduction of treatment effect when mediator is included), will we calculate the effect of mediation using MacKinnon and colleagues' product of coefficients method.(MacKinnon, Lockwood, Hoffman, West, & Sheets, 2002) Bias-corrected 95% confidence intervals for the mediated effect will be calculated using bootstrapping.(Shrout & Bolger, 2002)

6.12.2 Development of the recommendation engine algorithms will use machine learning and Bayesian statistical methods that will continuously learn that will continuously learn from user interactions with IntelliCare to provide intervention recommendations.

6.12.3 Exploration of moderating variables on outcomes, such as baseline demographics, baseline characteristics.

2.2.3 Explore, optimize, and validate coaching methods. This will include analyses of all data captured in the delivery of coaching, including the timing and content of messages and phone calls, and coach records related to participant encounters.

7 STUDY MANAGEMENT

7.1 Conflict of Interest.

7.1.1 Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by

Northwestern University Conflict of Interest Office. All investigators will follow the University conflict of interest policy.

7.2 Institutional Review Board (IRB) Approval and Consent

- 7.2.1 It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.
- 7.2.1.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.
- 7.2.1.2 Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an electronic IRB-approved consent form. On this consent form, participants will have additional opportunities to provide separate consent for: 1.) contact regarding future research opportunities and 2.) permission to use anonymous quotes from opinions they have expressed about the IntelliCare apps during the course of the study for use in the design of future digital interventions, promotional recruitment materials, Center for Behavioral Intervention Technologies website, research papers, presentations, and media stories.

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